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NEWS & ANALYSIS

Pharmaceuticals in the Environment: Regulatory and Nonregulatory Approaches

by Holly V. Campbell

This Dialogue explores the legal and regulatory implications of the discovery, through more precise detection technology, of the presence of pharmaceuticals and personal care products (PPCPs)[1] and endocrine disrupting compounds (EDCs) in the environment, particularly in surface water and public water supplies. The effects of drugs and hormones and other PPCPs on aquatic life, and the effects of unintended human exposure, are largely unknown.[2]

Drugs for treating infection, depression, seizure, and heart disease are being detected in surface waters around the United States. Synthetic estrogens are also being found, as are veterinary antibiotics and growth hormones. Although environmental pathways include point sources and nonpoint sources, researchers hypothesize that the main pathway of human treatment drugs and compounds into the water supply is through municipal sewage.[3] This is thought to be because most drugs are not completely metabolized so the excess and metabolites are excreted in urine and feces,[4] and because municipal treatment technology, much of it a century old, was not designed to remove these compounds.[5]

Nationwide concern is mounting regarding these compounds' trace presence in water. Recently, the news media have produced stories of drugs being detected in tap water in U.S. locations including Birmingham, Alabama,[6] Kansas City, Missouri,[7] and New Orleans, Louisiana.[8] This Dialogue examines, in light of unfolding research, whether these compounds' entry into the environment should be regulated to a greater extent than at present. The discussion is in three parts. The first part is a summary of current findings and concerns in the United States, where scientific inquiry into this issue is just beginning and in Europe, where the inquiry is now 10 years old. Part I includes a discussion of the compounds at issue, potential health risks to aquatic organisms and humans, and available information or hypotheses on synergistic effects.

Part II asks whether these substances' entry into both surface water and public drinking water should be regulated more stringently. This section includes a description of how agencies, particularly the U.S. Environmental Protection Agency (EPA) and the U.S. Food and Drug Administration (FDA) assess risk in the face of scientific uncertainty. Part II then examines what American regulatory structures are already in place, and which might be most suitable to remove PPCP contaminants and/or prevent further contamination.

Part III presents some proposals for regulation in and beyond the command-and-control structures now available.

Current Findings

Most observers agree that PPCPs and EDCs have probably been present in treated sewage since the beginning of their use. But it wasn't until the invention, and gradually less costly availability, of better detection equipment and associated methodology (largely mass spectrometry) that we even thought to look for what had previously been invisible.[9] To date, researchers have examined water for only a fraction of the tens of thousands of PPCP compounds and subcompounds that are known to exist.[10]

The pollution of most concern stems from PPCPs' use by consumers, which is ubiquitous and enters surface waters through municipal sewage systems. Important sources of PPCP pollution, such as manufacturing,[11] are already heavily regulated.[12] However, in the United States, 50 million pounds of antibiotics alone are produced each year, of which 60% are used for human illness and 40% for farm ani-

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1. PPCPs include unbiodegraded body care products, such as fragrances and sunscreen lotions. EPA, Office of Research and Development, Summary Background for PPCPs in the Environment 2, *available at* http:www.epa.gov/esd/chemistry/ppcp/review.htm [hereinafter Summary Background].
2. *See id.*
3. *See id.* at 1.
4. *See id.* at 3.
5. *See* U.S. EPA, Office of Research and Development, Frequently Asked Questions From the Public, Media, and Scientific Communities 2, *available at* http:www.epa.gov/esd/chemistry/pharma/faq.htm [hereinafter EPA FAQ].
6. *See* Katherine Bouma & Patrick Hickerson, *Old Water Tests, New Pollutants Worry Scientists*, Birmingham News, Nov. 19, 2000, *available at* http://www.al.com/news/birmingham/Nov2000/10-e419358b.html.
7. *See* Donald G. Wilkison, Pharmaceuticals and Other Wastewater Indicator Compounds in Two Suburban Streams, Address Before the American College of Toxicology 21st Annual Meeting (Nov. 14, 2000), *available at* http://www.epa.gov/nerlesd1/chemistry/ppcp/21st-overview.htm#.
8. *See* Mike Dunne, *Traces of Medicines Found in New Orleans-Area Water*, The Advocate, July 9, 2000, *available at* http://theadvocate.com/news/story.asp?StoryID=14574.
9. *See* Christian G. Daughton & Thomas A. Ternes, *Pharmaceuticals and Personal Care Products in the Environment: Agents of Subtle Change?* 107 Envtl. Health Persp. 912 (1999).
10. *See id.* at 925.
11. *See* EPA FAQ, *supra* note 5, at 9.
12. *See* Ranga Velagaleti et al., *Current Good Manufacturing Practices, Emission Regulations, and Guidances Minimize or Prevent Pharmaceutical Chemical Discharges From Entering Our Sources of Drinking Water*, Proceedings of Environment 2001: Water, Energy, and the Law, organized by the Tulane Institute for Environmental Law and Policy (Mar. 9, 2001) (unpublished paper received from Tulane) (on file with the author).

mals.[13] Every year, individual drugs are produced worldwide in quantities from kilograms to the hundreds of tons, while PCPs are manufactured in the thousands of tons.[14] Annual worldwide sales of medicines are estimated at $210 billion. The U.S. share of this figure is $92 billion. These numbers[15] are expected to grow as the development for new drugs meets the ever-increasing demand in the context of an increasing population that contains (especially in the United States)[16] a large, aging demographic subset.

Some toxicologists suspect that low-level, water-borne pharmaceuticals, some of which are known to be toxic, will cause subtle as well as latent harm, such as loss of intelligence quotient (IQ), behavioral changes, or other profound but gradually occurring changes similar to the documented effects of exposure to lead, mercury, and polychlorinated biphenyls (PCBs).[17] Some pharmaceutical traces that do not biodegrade in water have the ability to become active in the future, either in their original "parent" form (after being released by hydrolysis of metabolic conjugates) or by yielding bioactive transformation products from various environmental processes that alter their chemical structures, e.g., via sunlight. These parent compounds and bioactive products have the potential to be harmful alone or contribute to synergistic effects via multiple combined exposures. One particularly complex synergistic effect takes place when aquatic organisms adapt to surrounding pollutants over a long period of time, leading to the introduction of a new substance and a cascading toxic effect similar to sudden loss of toxicant tolerance in humans. According to Christian Daughton and Thomas Ternes, this process "can give the illusion that the toxicity potential in the . . . environment is stable or even decreasing when in reality it may be increasing."[18]

PPCP and EDC compounds span many disparate chemical classes.[19] Although they are not synonymous, some compounds fit in both categories.[20] For example, synthetic steroids are direct-acting EDCs, but only a small subset of PPCPs.[21] As with many other man-made chemicals that have entered the environment, a surprisingly large group of pharmaceuticals not specifically designed as synthetic hormones is turning out to exhibit endocrine-disrupting effects.[22]

Although PPCPs and EDCs are not currently part of any formal water-monitoring program in the United States,[23] surface water detection and research in the United States on PPCPs and EDCs is approximately three years old. The problem has been known and studied in Europe for a decade. American samples analyzed so far show that these substances, when detected, are mainly measurable in parts per billion (microgram per liter) and below in surface water, and in lower concentrations in public tap water.[24] In a Kansas City, Missouri, study, the U.S. Geological Service found that 40% of the area stream samples yielded detectable concentrations of pharmaceuticals and that 60% of the samples included triclosan, a common active ingredient in antibacterial hand soaps.[25]

Sewage is the primary point source for pharmaceuticals in water. Pharmaceuticals are not completely removed before the treated wastewater passes into surface waters.[26] It is important to add that, even in 2001, there were still an estimated one million homes, and even entire cities, that discharge sewage directly to streams. Even municipal sewage treatment works occasionally discharge raw sewage directly to surface waters during overflows due to heavy rainstorms or system malfunction, or during deliberate shutdown for maintenance and repairs.[27]

The most common sewage treatment technology was not designed to remove PPCPs[28] from domestic wastewater or to remove compounds inherent in runoff from agriculture. This two-pronged exposure is of concern to communities served by "combined" domestic/stormwater public sewage treatment systems, which were installed in our oldest cities at the turn of the 19th century. The problem can be exacerbated where treated water is recycled for drinking water, an increasingly common consideration as cities search for ways to augment their water supplies due to population strains on the available traditional sources.[29]

PPCP pollutants also come from nonpoint sources such as storm runoff, especially from areas where beef and dairy cattle, pigs, and poultry are raised.[30] In most high-production livestock operations animals are given hormones to speed growth, yielding larger animals, that are ready for market sooner.[31] The animals are also given large doses of antibiotics to prevent disease, particularly on so-called factory farms where the animals are kept in large numbers in close confinement, and where disease outbreaks would be catastrophic. This practice increases the presence of PPCPs in water, multiplying these substances' problematic effects.

13. *See* Kathleen Fackelmann, *Drugs Found in Tap Water*, USA Today, Nov. 8, 2000, *available at* http://www.usatoday.com/life/health/general/hgen115.htm.
14. *See* EPA FAQ, *supra* note 5, at 9.
15. *See id.*
16. *See* Velagaleti et al., *supra* note 12, at 4.
17. *See* Daughton & Ternes, *supra* note 9, at 934.
18. *Id.* "The resulting effects would be inexplicable if considered solely on the basis of exposure to the new toxicant." *Id.*
19. *See* Christian G. Daughton, *Pollution From Personal Actions, Activities, and Behaviors: Pharmaceuticals and Personal Care Products in the Environment; Multidimensional Science Issues Relevant to Regulatory Considerations* 2, Proceedings of Environment 2001: Water, Energy, and the Law, organized by the Tulane Institute for Environmental Law and Policy (Mar. 9, 2001) (unpublished paper received from Tulane) (on file with the author) [hereinafter Daughton, Tulane Proceedings].
20. *See* Christian G. Daughton, *Pharmaceuticals in the Environment—Overarching Issues and Concerns,* 40(1) Analysis of Environmental Endocrine Disruptors, Reprints of Extended Abstracts 96-98 (2000), *available at* http://www.epa.gov/esd/chemistry/pharma/ppcp-slides-mar-2.pdf or http://www.epa.gov/nerlesd1/chemistry/pharma/index.htm.
21. *See id.*
22. Examples include selective serotonin reuptake inhibitors altering spawning behavior of shellfish, and calcium-channel blockers inhibiting sperm production. *See* EPA FAQ, *supra* note 5, at 10. *See also* Dunne, *supra* note 8, at 3.
23. *See* Daughton & Ternes, *supra* note 9, at 934.
24. *See* Fackelmann, *supra* note 13; *see also* http://toxics.usgs.gov/highlights/whatsin.html.
25. *See* Wilkison, *supra* note 7.
26. *See* Daughton & Ternes, *supra* note 9, at 922.
27. *See id.* at 908.
28. *See id*. at 908, 922.
29. *See* Lindsey A. Greene, *Controversy Swirls Around Toilet-to-Tap Project*, 108 Envtl. Health Persp. 10 (2000).
30. *See* Daughton & Ternes, *supra* note 9, at 923.
31. *See* Fackelmann, *supra* note 13, at 2; Dunne, *supra* note 8, at 2.

An ancillary effect of antibiotics in farm animals is that humans may contract disease borne by bacteria in meat. The bacteria, now antibiotic-resistant, are thought to contribute to increasing episodes of public illness that have become gradually unresponsive to traditional antibiotic prescriptions.[32] One researcher at the U.S. Center for Disease Control (CDC) points out, however, that to date there is not enough proof that environmental exposure (as through antibiotic-tainted drinking water) is responsible, or could be responsible, for bacterial tolerance of antibiotics. He joins many in stating that the main cause of bacterial tolerance of antibiotics is patient abuse of antibiotic prescriptions, and (perhaps to a lesser extent) consumption of antibiotic-tainted meat which is undercooked.[33]

The effects of waterborne pharmaceuticals on aquatic life are only partially understood. For aquatic organisms, exposure to these compounds is continuous and unremitting. PPCPs are replenished in newly discharged wastewater before they can be removed by common, natural processes such as breakdown by microbes or sunlight.[34] Most PPCPs and EDCs[35] have never undergone laboratory studies for aquatic toxicity data,[36] although some data are available for antibiotics and antidepressants.[37] The main concern is that although pharmaceuticals' effects on aquatic organisms have gone unrecognized until now, the possibility exists that they could be responsible for certain otherwise unexplained toxic events, such as sudden massive fish die-offs, as well as more subtle problematic changes, including neurobehavioral and intelligence changes and physical deformities in fish.[38]

Canadian studies show that in the Great Lakes region endocrine disrupting hormones are likely to be responsible for fish developing both male and female characteristics.[39] It is also known from Canadian studies that traces of PPCPs in concentrations of 10 parts per trillion (ppt) in water alters development of fish; the same studies found that one form of estrogen used in birth-control pills "affected fish in concentrations as low as one part per trillion."[40] The detectable quantity of 10 ppt is one-third of the amount that scientists found in New Orleans area tap water and half the average amount detected in river and lake water in a study done by Tulane researchers.[41]

It is important to note that the FDA categorically excludes drugs from going through a National Environmental Policy Act (NEPA)-required environmental impact statement (EIS)[42] process if a drug, when on the market and prescribed or purchased over the counter and consumed, is not expected to enter the aquatic environment annually in concentrations exceeding one part per billion (ppb).[43] Moreover, aquatic organisms' physiology, including receptors that are activated or blocked by chemical pollutants, is completely different from human physiology. Thus, human exposure data (were it available) would likely have questionable relevance to the study of the impact on aquatic organisms.[44]

Although the aquatic toxicity studies are only beginning, the preliminary data provide reasons for caution. Crayfish, fiddler crabs, and other crustaceans; bivalves (such as clams); frogs; and fish and other lifeforms have been exposed to pharmaceutical concentrations which mimic the concentrations being detected in surface waters both adjacent to and nonadjacent to treated sewage effluent around the United States and Europe. Following is a small (and necessarily simplified) sampling of various drugs detected in surface and groundwaters with potential effects on aquatic life listed by easily recognized drug type (each type actually contains numerous subtypes). It should, of course, be borne in mind that potential effects, where even hypothesized, need to be studied and/or confirmed through controlled, peer-reviewed toxicity tests[45]:

common name	potential effects
antibiotics	observed antibiotic resistance in stream bacteria, and in geese
antidepressants	early spawning
blood lipid regulators	unknown
some analgesics and anti-inflammatory beta-blockers	collagen metabolism in fish stimulates ovaries and accelerates testicular maturation in crabs and shellfish
anti-depressants/SSRIs	elicits early spawning in mussels
anti-epileptics	unknown
antineoplastics (chemotherapy)	nonreceptor specific; considered genotoxic and have potential as mutagens/carcinogens/teratogens/embryotoxins
impotence drugs	unknown
tranquilizers	unknown
retinoids	observed amphibian deformities
x-ray media contrast agents	potentially harmful; no observed effects at 10 g/L

Throughout his research, Daughton has continually pointed out the difficulties of practically assessing risk inherent in these compounds' presence in water because of the

32. *See* Fackelmann, *supra* note 13, at 3.
33. *See id.*
34. *See* Daughton & Ternes, *supra* note 9, at 934.
35. The substances at issue include many synthetic and natural hormones whose terminology includes environmental estrogens, endocrine-disruptors, endocrine-modulators, ecoestrogens, environmental hormones, xenoestrogens, hormone-related toxicants, hormonally active agents, and phytoestrogens.
36. *See* EPA FAQ, *supra* note 5, at 8.
37. *See id.* Other examples of classes that have existent data include antiepileptics, some shown to be neuroteratogens, and chemotherapy media, which are "acutely genotoxic."
38. *See* Jean Raloff, *Excreted Drugs: Something Looks Fishy*, Sci. News, June 17, 2000, *available at* http://www.sciencenews.org/20000617/fob1.asp.
39. *See id.*
40. Dunne, *supra* note 8.
41. *See id.*
42. 42 U.S.C §4332(C), ELR Stat. NEPA §102(C).
43. *See* Nancy B. Sager, *FDA's Statutory Framework and the Evaluation of Pharmaceuticals for Potential Environmental Impact*, Proceedings of Environment 2001: Water, Energy, and the Law, organized by the Tulane Institute for Environmental Law and Policy (Mar. 9, 2001), *available at* http://www.epa.gov/nerlesd1/chemistry/ppcp/21st-overview.htm#FDA's Statutory Framework/.
44. *See* Daughton, Tulane Proceedings, *supra* note 19, at 7.
45. *See* Daughton & Ternes, *supra* note 9, at 927-30

widely varying effects on numerous species and subspecies and the tens of thousands of compounds and subcompounds with vastly differing dosages and abilities to re-aggregate with other compounds in the environment. For example, data for one species of clam cannot be extrapolated for a species of mussel, even given laboratory exposure to a single compound at controlled dose. Or, to cite another example, regarding serotonin Daughton writes: "It is clear that aquatic life can be exquisitely sensitive to at least some of this class of compounds. Although some SSRIs [selective serotonin reuptake inhibitors] are extremely potent, others have almost no effect, which possibly makes the approach of assessing ecologic risk on a class-by-class basis infeasible."[46]

Regulatory Options

To lessen and eventually cease the constant reintroduction of PPCPs into the environment should be a goal.[47] A logical means of achieving this goal is environmental regulation. Normally, before regulatory solutions are applied to an environmental problem, agencies must establish at least preliminary information about risk, based upon scientific data indicating which classes of PPCP compounds pose the greatest harm, in what quantities, to the most sensitive aquatic and human populations. The following section provides a brief background of how EPA and FDA incorporate the assessment of risk into their regulatory decisionmaking.

Risk and the Unknown

Risk effects all of us and we all engage in it voluntarily and involuntarily daily. But most of us would agree that we prefer to choose our own known risks than be exposed to the unknown against our will, and that unless we are professionals trained in a field involving risk calculation, we do not know enough as citizens to examine or address most of the involuntary risks we daily encounter. Current environmental problems such as PPCP contamination challenge us to increase our knowledge of the various risks we are creating through the lives we daily lead in a prosperous, developed nation. Citizens, policymakers, and lawyers all need to become more sophisticated in their understanding of risk.

The American environmental statutory structure is replete with examples of attempts to manage risk, including indeterminate risk, using regulatory mechanisms. The chemical product revolution in the United States since World War II created many risks, some of which were anticipated and studied, such as the small subset of substances commonly referred to in both the air and water pollution control statutes as "conventional pollutants."[48] Other risks went unrecognized with deleterious effects emerging slowly until finally the causes were identified (such as in the cases of dioxin, benzene, and asbestos).[49] It seems likely that PPCPs and EDCs in the environment are of that class that present a great challenge to our ethical, legal, and medical structures, as they exemplify the problem of latent harm from chemical, environmental insult. This harm can take a decade or half a human lifetime to emerge as anthropogenic suffering.

Knowledge that there are pharmaceuticals in the environment is troubling to the public, scientists, environmentalists, and the legal community. The problem exists, thus far, on the edge of the regulatory system. The question of how to assess risk in the face of scientific uncertainty is at the heart of the controversy over pharmaceuticals in water. Yet, inquiries seeking to assess risk in the face of scientific uncertainty are familiar; we undertake them in relation to EPA's approval for manufacture of new pesticides, herbicides, rodenticides, and fungicides[50]— at least with regard to some of those formulations' most common, and most toxic, constituents.[51] Traditional risk assessments might apply to the issue of pharmaceuticals in water as well.

In assessing risk, perhaps we are by now better at knowing what complex web of questions to ask. Arguably, however, the universe of risk is both expanding and metamorphosing while we try to map and assess small, circumscribed areas within it. As background, it is useful to look at how the National Research Council conceived of risk assessment in 1983, and then examine more contemporary views of risk by the National Academy of Science in 1993, and the concept of the "Risk Cup" as elaborated upon by Daughton, Chief of the EPA Environmental Chemistry Branch in Las Vegas in 2001. Each of the three views is highly complex and goes into far greater detail than the space of this text permits. The purpose of the comparison is to demonstrate how subjective risk assessment can be, and how contextual and dependent upon the conscientiousness and expertise of the assessment's author(s) and how general or specific their objective. Therefore, it is not enough to assess what levels of risk did the assessment of problem X yield; we must examine who assessed problem X, using what model, and with what expertise and assumptions. The objective exposure level sought (morbidity, cancer level, deformities, neurobehavioral changes, slighter nuances of interference) also makes a difference in how one interprets the data obtained. These questions must be addressed before we even get to the data on the subject contaminant. Ultimately, most risk assessments remain only a guideline, riddled with the unknown.

46. *Id.* at 928.

47. *See id.* at 912.

48. Statutory "conventional" pollutants in air include carbon monoxide, sulfur dioxide, nitrogen oxides, volatile organic compounds, particulates, and lead, *see* 42 U.S.C. §7408, ELR STAT. CAA §108, and in water include biological oxygen demanding pollutants, suspended solids, fecal coliform, and pH (hydrogen ion concentration), *see* 33 U.S.C. §1314(a)(4), ELR STAT. FWPCA §304(a)(4).

49. It has been established that effects of exposure to these pollutants include a higher risk of leukemia (benzene and dioxin) and lung cancer (asbestos).

50. *See* Toxic Substances Control Act, 15 U.S.C. §§2601-2692, ELR STAT. TSCA §§2–412, and the Federal Insecticide, Fungicide, and Rodenticide Act, 7 U.S.C. §§136-136y, ELR STAT. FIFRA §§2–34.

51. *See* Daughton & Ternes, *supra* note 9, at 912. They point out that the distinction between pesticides' (for example) and PPCP/EDCs' entry into the environment is one of diffusion and ubiquity as the PPCPs are used by individuals, with evidence suggesting that drugs are sometimes disposed of wholesale, never having been opened or used, by disposal through flushing down the toilet or deposit into landfills.

Features of Some Recent Models of U.S. Risk Assessment[52]

National Research Council 1987
employs three lines of inquiry:
hazard identification—cause and effect relationship
dose-response assessment—probability of a hazard
exposure assessment—how many people exposed at what levels
to characterize risks either qualitatively (is risk great or small) or quantitatively (population at risk) leading to risk comparison inquiry
Criticisms include: lack of human data and nontransferability of animal data, lack of data on biological mechanisms of harm; results vary widely depending on methodology (as in dose-response); endpoint is usually morbidity or cancer, information ultimately of limited use for prevention
National Academy of Sciences 1993
retained maximum tolerated dose (MTD), criticized because increased cell division resulting from carcinogen exposure also contributes to mutation of cells (mitogenesis leads to mutagenesis; hotly debated); note that mechanisms are now included in scrutiny
Daughton, "Risk Cup," EPA Chemistry Branch, 2001[53]
incorporates views and questions from biochemical perspective, and places at forefront, instead of placing regulatory/policy perspective first; seeks to locate, study, and understand biological mechanisms (or modes) of action through which chemical substances turn on, turn off, or otherwise interfere with receptor cells and their normal processes
pragmatically considers and seeks to include in risk assessment realities of multiple effects, synergism/antagonism, aggregate exposure, complementary exposure, cumulative exposure, and observable/replicatable phenomenon of Hormesis: "Paradoxical or unanticipated effect at low doses" and other biological effects of low-level exposure (BELLE)
note that this approach is getting at the biology of risk by laying out preliminary questions cogent to a thorough investigation, while the science to get there develops apace; former criticisms of other models above included statements by policymakers to the effect that "the science wasn't there yet," as in response to proposal that the Classic Model should drop MTD

The National Research Council model is currently in use at EPA; Daughton's work is included here as a suggestion of where risk analysis might be headed. As Daughton and Ternes have suggested:

> There are two debates in the realm of ecotoxicology, both of which have ramifications with respect to performing ecologic risk assessments (ERAs) for PPCPs. The first is the relevance of purposefully simplified, defined-species toxicity tests to predicting/extrapolating pollutant impacts on the more highly organized and complex structural/functional levels of communities or ecosystems (processes) (citing Boudou and Ribeyre); this is truer for PPCPs than for pesticides, as the former were generally never designed to have any intended effects on wildlife and therefore any knowledge as to what types of effects to look for is clearly more limited. Can changes in a complex system be predicted from knowledge of a small subset of the underlying components? The second is the question of whether it is necessary to know the spectrum of possible physiologic effects, given a multitude of organisms, or possible mechanisms (modes) of action before looking for and ascribing causation to changes at the population level and higher. Considering this, one can only pose at this time the rhetorical question as to whether the risk posed by the presence of pollutants in complex waste streams . . . can be detected/quantified by the use of current toxicity screening tests never designed to embrace the spectrum of end points (some exquisitely subtle) that may be involved. The most conservative approach would be one that captures the coordinated use of toxicity-directed screening and chemistry–directed screening and chemistry-directed characterization, feeding the results of each to the other, to better reveal the nature of any stressors.[54]

Before we can assess the risk that the presence of the various PPCP and EDC compounds and subcompounds pose in the environment, we must have sound scientific data on these substances' effects on aquatic life and humans in low doses. As recently as November 2000, an EPA water office official stated that there is "far too little data [yielded from dose-response studies of PPCPs on aquatic life] to even conduct a risk assessment at this time."[55]

The FDA considers risk in at least three ways.

> Environmental impact. Applicants for approval to manufacture new drugs must follow a 1998 FDA guidance document that requires the applicant to determine whether the concentration of the active ingredient in the drug expected to enter the aquatic environment exceeds one ppb.[56] If the applicant determines, through an FDA-derived formula, that the concentration will enter the environment at less than one ppb, applicants are granted a categorical exclusion from the requirement of preparing an EIS.[57]
>
> "Single dose acute[58] toxicity testing." The drug industry must conduct this type of testing on animals for any drug intended for human use through procedures recommended in a 1996

52. *See generally* Robert V. Percival, Environmental Regulation: Law, Science, and Policy 427-516 (3d ed. 2000).

53. Daughton, Tulane Proceedings, *supra* note 19, at 13.

54. Daughton & Ternes, *supra* note 9, at 923.

55. Octavia Conerly, *Pharmaceuticals in the Environment—A Perspective From EPA's Office of Water*, Proceedings of the American College of Toxicology 21st Annual Meeting (Nov. 14, 2000), *available at* http://www.epa.gov/nerlsesd1/chemistry/ppcp/21st-overview.htm#.

56. *See* 21 C.F.R. §25.31.

57. *See* Sager, *supra* note 43; *see also* Velagaleti et al., *supra* note 12.

58. Some toxicologists state that acute testing is not enough, but that chronic testing must also be undertaken if ecological risk assessments are to be meaningful. *See* Daughton & Ternes, *supra* note 9, at 934.

guidance document.[59]

> Testing of drugs' fate and effects if the need for an EIS is triggered. The fate and effects testing begins with acute testing,[60] recommends (does not require) aquatic organisms over terrestrial for use in testing, and is based on an approach used by EPA.[61]

Having examined three current models of risk assessment, the paper will turn to existing regulatory options to determine if they are of use for reducing or eliminating PPCPs in water.

Sufficiency of Existing Regulations

For the narrow purposes of this Dialogue, we will agree with observers who state that drug manufacturers' wastewater discharges are well regulated as a discrete categorical point source[62] of pollution and are not the main contributor to PPCP pollution. At least some scientists from the industry side say that regulations spanning the entire lifetime of pharmaceuticals from manufacture through disposal reduce or eliminate PPCPs and EDCs in drinking water.

> Compliance with . . . FDA and EPA regulations and guidance . . . for pharmaceutical chemical discharges from manufacture, use and disposal prevent . . . drugs from entering sources of drinking water in the United States and causing any risk to human health. The authors believe that neither additional treatment of drinking water sources over and above existing now, nor new regulations are [sic] required. In the rare event of pharmaceutical chemical residues being detected in drinking water supplies using available analytical technologies, establishment of a clear cause and effect relationship investigations [sic] are required to explain unusual circumstances that may have resulted in the detection of such residues [circumstances which] may include noncompliance with existing regulations or accidental discharges. They also include confusion with chemical residues originating from agrochemicals and personal care products that are used in large quantities and have more potential for environmental exposure than human and animal health drugs because of their use patterns.[63]

Notably, the authors of the above excerpt, scientists with BASF Corporation, also state that pharmacies, hospitals and clinics, as well as ordinary citizens, should dispose of empty or partially empty containers of drugs through proper collection procedures or certified landfills, eliminating disposal as a source of environmental contamination.[64] The authors state that compliance with existing regulations avoids PPCP water pollution. The authors also assert that PPCP pollution is therefore caused by noncompliance with existing regulations and confusion over chemical identification. It is possible that such a proposition includes the desire to be free of more onerous regulatory responsibility and its associated expense. Regardless, the assertion that regulations are currently adequate is inaccurate because it avoids the empirical evidence that PPCPs and EDCs that have been specifically identified,[65] are harming aquatic biota in concentrations smaller than the one ppb, the level at which the FDA considers qualification for the EIS categorical exclusion.

The FDA

The FDA's regulations contain the following provisions:

> The classes of actions listed in this section are categorically excluded and, therefore, ordinarily[66] do not require the preparation of an EA [environmental assessment] or an EIS . . . .
>
> (b) Action on an NDA [New Drug Application], abbreviated application, or a supplement to such applications . . . if the action increases the use of the active moiety [or active ingredient] but the *estimated* concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.[67]

In 1995, the FDA conducted a retrospective review of aquatic toxicity studies on hundreds of new drugs approved in the period 1985-1995 that had generated findings of no significant impact (FONSIs).[68] Because of the repeated FONSIs, in July 1997, the FDA formalized its position regarding the environmental effects of new drug approval in the categorical exclusion noted in 21 C.F.R. §25.40. The following regulatory provision suggests that when the environmental assessment (EA) reviewing the approval of new drugs was undertaken, the "tiered approach" to testing came into play to justify the FONSI:

> (a) If potentially adverse environmental impacts are identified . . . the EA shall discuss any reasonable alternative course of action that offers less environmental risk or that is environmentally preferable to the proposed action. The use of a scientifically justified tiered testing approach, in which testing may be stopped when the results suggest that no significant impact will occur, is an acceptable approach.[69]

The following provision regarding parallel timing of an EIS and drug approval begs the question of whether an EIS would ever seriously trigger a hard look[70] by the

59. *See* FDA, Center for Drug Evaluation and Research, Guidance for Industry: Single Dose Acute Toxicity Testing for Pharmaceuticals (1996). Guidance documents do not have the legal status of regulations; nor are they subject to public notice-and-comment rulemaking before being published in the *Federal Register*. The single dose acute toxicity testing guidance, itself, bears notice (in a footnote) that the guidance binds neither the FDA nor industry, but merely represents the FDA's views on the subject.

60. Acute testing measures a substance's ability to cause toxic effects (including death) at low doses or short exposure. *See* Percival, *supra* note 52, app. A, at 1239.

61. *See* Sager, *supra* note 43.

62. *See* 40 C.F.R. §439.

63. Velagaleti et al., *supra* note 12, at 3.

64. This is in direct contradiction to common knowledge about the practice of flushing drugs down the toilet to dispose of them "safely." The authors do not comment on the potential problem of groundwater contamination from landfill disposal. In a Danish landfill, leachates have been discovered from over 45 years of disposal. *See* Daughton & Ternes, *supra* note 9, at 923.

65. *See id.* at 913-21.

66. The exceptions are for drugs expected to enter the aquatic environment in quantities greater than one ppb or drugs made from wild plants. *See* Sager, *supra* note 43.

67. 21 C.F.R. §25.31 (emphasis added).

68. *See* Sager, *supra* note 43.

69. 21 C.F.R. §25.40.

70. In a process much like that described by Judge Harold Leventhal, which courts must use to review agency decisions to make sure that the agencies (1) abided by fair and reasonable procedures, (2) gave good-faith consideration to matters assigned to them, and (3) pro-

agency at its alternatives, including disapproval of a new drug application:

> (a) If FDA determines that an EIS is necessary for an action involving investigations or approvals of drugs, . . . an EIS will be prepared but will become available only at the time of the approval of the product. . . .
>
> (b) Comments on the EIS may be submitted after the approval of the drug. . . . Those comments can form the basis for the agency to consider beginning an action to withdraw the approval of applications for a drug . . . or to withdraw premarket notifications or premarket approval applications for devices.
>
> (c) In those cases where the existence of applications and premarket notifications for drugs . . . has already been disclosed before the agency approves the action, the agency will make diligent effort . . . to involve the public in preparing and implementing the NEPA procedures for EISs while following its own disclosure requirements including those listed in part 20 . . . of this chapter.[71]

The lack of consideration given to the significance and cumulative effects of the impacts of introducing new drug compounds into the environment is troubling. The use in the formula of the expected introduction of the active ingredient into the aquatic environment of solely one year appears to seriously undercalculate the larger impact over time. A NEPA-required consideration of significance and cumulative effects would seem to necessitate a longer look—certainly more than one year. The tiered approach fate and effects testing, which is patterned after EPA, is statutorily avoided when there is a categorical exclusion in place. The categorical exclusion resulting from the repeated FONSIs, and formalized in the 1997 EA from the retrospective review, has created a discrepancy between FDA's regulations and NEPA. This is troubling to ecotoxicologists such as Daughton (EPA), and Ternes (Institute for Water Research and Water Technology, Wiesbaden-Schierstein, Germany) who state that not considering cumulative (whether additive, synergistic, or antagonistic) effects of multiple compounds targeting the same bioreceptors is "a significant shortcoming." They further state that

> [t]he EEC [expected environmental concentration] value for any given drug could easily be exceeded when the cumulative concentrations of like-mode-of-action drugs are considered, especially in those instances where numerous competing drugs are commercially available in any class. . . . [T]his approach also ignores the possibility of synergistic effects from drugs of other classes.[72]

A consideration of cumulative effects[73] is especially relevant with regard to PPCPs because of their highly variable, wide-ranging biologic modes of activity. Many PPCPs apparently do not break down completely, by human metabolism, microbes, sunlight, and so forth, and many others either persist in the environment, or mimic persistent compounds due to constant reintroduction before any chance of biodegradation. There are also compounds that persist mainly because they are fat soluble, and therefore tend to bioaccumulate in tissue.[74] Some trace compounds can actually become active again and recombine or form conjugates with other compounds.

Another problematic factor is that the applicant for approval to manufacture the new drug is charged with testing it,[75] by methods which the FDA recommends but does not require.[76]

EPA

The Clean Water Act (CWA) and Sewage Treatment Works

Publicly owned treatment works (POTWs) are subject to the CWA permitting requirement under the national pollutant discharge elimination system (NPDES). POTWs treat at least 173 million Americans' sewage.[77] However, the installation of sewage pipes to service increasing residential, commercial, and industrial developments has outpaced the upgrading of the facilities' capacity and treatment technology.[78] Jackson Battle and Maxine Lipeles point out:

> At once, [POTWs] are both regulated entities, as most of them discharge treated wastewater into surface waters, and regulators, as they are obliged by federal and (in most cases) state law to impose and enforce controls on indirect dischargers who, by definition, discharge not to the surface waters but to POTWs. Further complicating the POTWs' [CWA] role is the fact that, as public entities, they generally do not control their funding sources; their efforts, both to comply with their own treatment obligations, as well as to enforce the obligations of indirect dischargers, have historically been underfunded.[79]

duced results that are defensible in reason. Harold Leventhal, *Environmental Decisionmaking and the Role of the Courts*, 122 U. Pa. L. Rev. 509, 511 (1974).

71. 21 C.F.R. §25.52.

72. Daughton & Ternes, *supra* note 9, at 936.

73. Ironically, were an EIS required before approval of a new drug, *cumulative impacts* to the environment of the introduction of the new compound would have to be addressed, defined as "the impact on the environment which results from the incremental impact of the action when added to other past, present, and reasonably foreseeable future actions regardless of what agency (Federal or non-Federal) or person undertakes such other actions." 40 C.F.R. §1508.7.

74. Including blood lipid regulators, *see* Daughton & Ternes, *supra* note 9, at 927.

75. *See* Sager, *supra* note 43. Aside from the possible bias involved, the science on this issue is hindered by using a pattern-book formula, which is seriously flawed because it is not empirically related to the amounts of PPCP compounds actually detected in the environment and actually shown to be causing harm. *See also* Deborah G. Parver, *Expediting the Drug Approval Process: An Analysis of the FDA Modernization Act of 1997*, 51 Admin. L. Rev. 1249 (1999) (detailing recent regulatory changes); Patrick A. Malone, *The Role of FDA Approval in Drug Cases*, 34 Trial 28 (1998) (products liability perspective); and Lauran Neergaard, *FDA Red Tape Not Slowing New Drugs*, Salt Lake Trib., Aug. 20, 2001, at A1.

76. One source suggests there is an inherent conflict of interest when an agency is faced with assessing the impact on the environment (through the requirement of a NEPA-mandated EIS) of a project or a product for which the agency, itself, is a major proponent. There exist potential issues of conflict of interest on both the applicant's part (aquatic testing to result in less than one ppb) and in the agency's part (funding, lobbying, political pressure by powerful industry interests). *See* Percival, *supra* note 52, at 904. One would logically wish to know, for example, if there is pressure from inside or outside the agency to approve and release the drug, and also where any financial interest and benefit lay.

77. *See id.* at 695.

78. The federal government spent $66 billion on POTWs from 1972-1997 resulting in a decrease in their discharges from 4 million to 4.3 million tons of waste per day. However, during this period the population that POTWs serve increased from 90 million to 160 million people, requiring an estimated additional $140 billion through the year 2017. *See* Jackson B. Battle & Maxine I. Lipeles, Water Pollution 335 (3d ed. 1998) (citations omitted).

79. *Id.* at 333.

As facilities age, so does the filtering technology (most American facilities use sand filtration),[80] the testing methods (mainly to detect fecal coliform), and the treatment method (largely with chlorine).[81] These predominant methods for sewage treatment are about a century old.[82] Surely, uncertain funding, an overloaded design capacity, and 100-year-old purification and evaluation technology are contributors to any problem involving contamination in surface waters coming from "treated" wastewater additions.[83]

POTWs are not mandated to subject municipal sewage to a primary[84] standard requiring the "best practicable control technology currently available." In fact, the CWA does not specify technology-based sewage purification standards. The Act does provide a qualification that states that a specific standard applies to various effluents that are not POTWs.[85]

Consider the assumptions likely underlying this exception. (1) Through the benefit of initiatives of the federal government beginning in 1956, and continuing by virtue of the Act's subchapter II in 1972, the federal government was providing grants[86] to local townships and municipalities for construction of sewage treatment plants because they were resisting, avoiding, or unable to build them or keep up with the demand for new ones on their own.[87] Rather than imposing an unpopular and potentially expensive standard on localities, the government and later EPA reasoned it could have a hand in growing and encouraging the proper technology through the grant funds administered. (2) Or until the 1950s, roughly, the composition of the nation's municipal sewage would have seemed rather innocent and predictable. It was unlikely that anyone thought ahead to the inevitable results of the burgeoning presence, over the ensuing 50 years, of tens of thousands of chemical compounds in the environment.[88] Communities were more concerned about screening out very particular, more obviously dangerous pollutants in wastewater from facilities producing other industrial byproducts (for example, ionizing radiation generated by the cold war nuclear weapons industry).

Instead of technology-based standards, POTWs[89] are required to treat sewage to secondary standards.[90] This choice of a less stringent standard is based upon the regulatory assumption that POTWs are engaged in eliminating "conventional pollutants," from wastewater which include removing suspended solids, fecal coliform, and monitoring for pH (hydrogen ion concentration). Though this assumption (underlying the requirement of secondary treatment of sewage) served societal needs for a long time, it is no longer valid due to the high volume of substances other than "conventional pollutants" that are entering the system.[91]

The Safe Drinking Water Act (SDWA)

The SDWA[92] has some promise for regulating and preventing PPCP contamination in drinking water, as a subset of surface water. The SDWA gives states minimum guidelines for setting maximum contaminant level goals (MCLGs) and maximum contaminant levels (MCLs) for certain substances found in drinking water.[93] EPA also plays a role in setting standards under the SDWA, although by 1995 EPA was to have promulgated standards for 83 substances, and has now identified standards for only approximately 67 substances.[94] One provision of the SDWA, the "Estrogenic Sub-

80. *See* Fackelmann, *supra* note 13, at 2.

81. *See* Bouma & Hickerson, *supra* note 6. They critique the use of fecal coliform as an indicator because (1) coliform bacteria's connection with human and animal waste is a loose connection, (2) some (even lethal) pathogens or parasites can be present when coliform is not, and some of those are resistant to treatment with chlorine, and (3) coliform itself does not always indicate presence of fecal waste.

82. *See generally id.*

83. In considering the problems of an overwhelmed POTW system, add to the antiquated water intake and delivery system the historically weak link of enforcement of pretreatment standards for so-called indirect dischargers, which are nonresidential (including industrial) dischargers that send their wastewater to POTWs. According to EPA, approximately 31 of 42 NPDES states also have approved pretreatment programs, and 1,600 POTWs (around 10% of the nation's POTWs) are required to use and enforce pretreatment programs. These 1,600 POTWs receive about 30 billion gallons of sewage per day, which EPA estimates is about 80% of national wastewater flow, as of November 1999. *See also* Battle & Lipeles, *supra* note 78, at 372, and Percival, *supra* note 52, at 697.

84. *See* 33 U.S.C. §1314(b), ELR Stat. FWPCA §304(b).

85. For example, 40 C.F.R. §§301(a)(2)(A); 304(b)(1)(A), (B), (2)(A), and (4)(A) and (B).

86. It is estimated that the U.S. government, states, tribes, and local governments have spent almost $100 billion to construct the thousands of sewage treatment plants (now full). *See* Percival, *supra* note 52, at 694.

87. The resistance plausibly stemmed from 150 years of gradually waning practice of piping sewage to the nearest waterway, and the reluctance to spend a lot of public tax money to benefit downstream populations. *See id.* at 695.

88.

> There are 80,000 different man-made chemicals that have been registered with the EPA for possible use in commerce. Of those 80,000, there are about 15,000 that are actually produced each year in major quantities, and of those 15,000, only about 43 percent [6,450] have ever been properly tested to see whether or not they can cause injury to humans.

Trade Secrets: A Moyers Report (PBS television broadcast, 2001) (quoting Dr. Philip Landrigan, Chairman, Preventive Medicine, Mt. Sinai School of Medicine, *available at* http://www.pbs.org/tradesecrets/transcript.html; clarification added). *See also Study of Toxins in Humans Offers Good, Bad News*, Salt Lake Trib., Mar. 22, 2001, at A1.

89. In 1997, EPA noted that the number of POTWs treating wastewater beyond secondary standards had risen from 22% in 1988 to 28% in 1996. *See* Battle & Lipeles, *supra* note 78, at 335.

90. *See* 33 U.S.C. §1311(b)(1)(B), ELR Stat. FWPCA §301(b)(1)(B); originally, the 1972 CWA would have required more advanced treatment (best practicable waste treatment technology) beginning in 1983. However, in 1981 Congress cancelled the advanced treatment requirement for POTWs. Stricter standards *may* be applied if dictated by water quality standards. *See* Percival, *supra* note 52, at 695.

91. An ancillary problem ensued when indirect (industrial) dischargers increasingly took advantage of discharging to POTWs rather than to surface waters, in "integrated" sewage systems referred to in the CWA, 33 U.S.C. §1281(e), ELR Stat. FWPCA §201(e) (which encourages the integration in order to generate revenues for the regional waste management agency to spend on "other environmental improvement programs"). It must be kept in mind that the pretreatment of the industrial "indirect" discharger, while held to a higher standard, was for a long time not well enforced. Indirect discharges to POTWs are relevant to the problem of PPCP pollution because they generate a high volume of industrial waste (subject to unevenly enforced advanced treatment standards), which adds to an overload of municipal wastewater only processed at secondary standards designed to remove "conventional" pollutants, not including chemicals or toxics. Thus, the CWA's provisions for POTWs are of potential (but at present, limited) use in addressing PPCP pollution.

92. 42 U.S.C. §§300f to 300j-26, ELR Stat. SDWA §§1401–1465.

93. States have primary enforcement authority and must report annually on these levels (§300g-3, ELR Stat. SDWA §1414) which include inorganic chemicals (regulated by MCLGs set forth in 40 C.F.R. §141.11), organic chemicals (regulated by MCLGs set forth in 40 C.F.R. §141.61), and other contaminants.

94. *See* 21 U.S.C. §346a(p)(3)(B).

stances Screening Program,"[95] gives the EPA Administrator the discretionary authority to test for new substances (not on the MCLG list) that may be found in drinking water, by using testing procedures outlined in the provision that list the other regulated contaminants, if the Administrator "determines that a substantial population may be exposed to such substance."[96]

A citizen's civil action provision in the SDWA[97] includes the right of any person to file a civil action against any person, including the United States, who is alleged to be violating the Act, or against the EPA Administrator if he/she allegedly failed to perform a mandatory act or duty. The U.S. district courts have jurisdiction, regardless of amount in controversy or the parties' citizenship. There is a 60-day notice period before a plaintiff may sue, and an exception for due diligence if the Administrator, Attorney General, or state has commenced an action to compel compliance.

The SDWA's evolution since its enactment has been very slow. The legislation has a powerful feature in its 1986 Amendments that requires any proposed MCL for a synthetic organic chemical to be "at least as stringent as the levels achieved by granulated activated carbon filtration." Economic and technologic feasibility must be considered[98] when setting these levels.

Proposals and Conclusion

As previously stated, only a fraction of possible waterborne PPCPs have been looked for. Attempting a full investigation of the tens of thousands of pharmaceuticals in use would be daunting in terms of expense, time, technical expertise, and the state-of-the-art technology required to reliably detect PPCPs in the ppb and ppt range. The PPCP problem is expected to grow through population growth and the growth of an aging demographic subset that will comprise a group which statistically consumes a larger quantity of medicines and medical services, and the ever-increasing demand for more and better drugs.[99] Further, with regard to some compounds, deformative effects are already taking place (in fish, for example) at more dilute concentrations than the less than one ppb FDA categorical exclusion to NEPA. Current standards are not protective enough, given what we already know is out there and the expectation of greater consumption, excretion, and disposal. It follows that if toxic effects are currently taking place in fish exposed at more dilute levels than one ppb, then the allowable concentration of these compounds in water should be lowered by law.[100]

The United States has environmental regulations that could address this issue. The NEPA procedure for preparation of an EIS whenever a government action will have an impact upon the environment is an important safeguard that should be honored. The FDA's approval of new drugs is a federal action that has environmental consequences. Industry and the FDA would most likely object that EISs can delay a product or project for months, even years, and that the necessary aquatic toxicity testing is prohibitively expensive, as well as impractical or even impossible. And perhaps industry and the FDA would be persuasive in their arguments against mandating a full environmental review before approval of every new drug. However, consider the alternative, in which society bears the greater costs in a later-stage, reactive mode. Several seemingly intractable environmental problems[101] were addressed in the last 50 years after complaints by industry that their new mandates of responsibility were unreasonable and impossible. Through sustained effort and creativity, PPCP pollution is similarly not intractable, even in the face of the uncertainties of present science.

NEPA features a provision on uncertainty (in 40 C.F.R. §1502.22) that contains the mandate to examine "reasonably foreseeable" impacts, which include potentially catastrophic impacts whose probability of occurring is low. It is reasonably foreseeable, due to the increased quantity, variety, and synergistic effects of these compounds, that they will inevitably become more dangerous, with potentially catastrophic impacts on health. Therefore, while we gather the data—it could actually take decades—the U.S. Congress should strongly consider amending the FDA's provision regarding the categorical exclusion relating to the agency's approval of all new drugs.

It is in the agencies' and the public's best interest to obtain and disseminate good, objectively derived data and to treat all recognized forms of pollution proactively (which is also more economical in the long term). Besides aquatic toxicity studies conducted during new drug review, the CWA itself may offer support of research through EPA. The CWA contains a provision for funding and technical support[102] that includes providing support to individuals and the general public for such activities as: "Research, investigations, experiments, training, demonstrations, surveys, and studies relating to the causes, effects, extent, prevention, reduction, and elimination of pollution." The detection of PPCPs is taking place largely through university and high school teachers and their students creating proactive, public involvement. The effort to get good and widely geographically dispersed data must be expanded with financial and technical support continuing from EPA, the U.S. Geological Service, and universities. Using a scientifically defensible body of aquatic

95. Promulgated in July 1994, the provision was added in August 1996. 42 U.S.C. §300j-17, ELR STAT. SDWA §1457.

96. *Id.*

97. *Id*. §300j-8, ELR STAT. SDWA §1449.

98. *Id*. §300f(1)(C), ELR STAT. SDWA §1401(1)(C).

99. Daughton and Ternes note that as the human genome is mapped, the discovery of more biochemical receptors will greatly expand the reach of pharmaceutical design up to twentyfold (from the currently recognized 500 biochemical receptors in the human body). Daughton & Ternes, *supra* note 9, at 934. Other researchers predict that the discovery of more specific receptors through studying the human genome may actually help lessen the problem of PPCPs in the environment because the targeting of more specific receptors should decrease the impact on unintended receptors, at least in humans. *See* Sally Deneen *Many Rivers to Cross: What Are Genetically Engineered Drugs Doing in Our Water Supply?* emagazine.com, *available at* http://www.emagazine.com/january-february_2001/0101feat1sb2.html at 2.

100. The CWA's goals and policies are "restoration and maintenance of chemical, physical, and biological integrity of [the] Nation's waters," which includes the goal of "water quality which provides for the protection and propagation of fish, shellfish, and wildlife . . . ." Other pertinent goals include a national policy to develop waste treatment management and technology to "assure adequate control of pollutants in each State," 33 U.S.C. §1251(a), (2) & (5), ELR STAT. FWPCA §101(a), (2) & (5).

101. For example, the reduction of automobile emissions mandated to industry through the CAA. *See* PERCIVAL, *supra* note 52, at 604-14.

102. *See* 33 U.S.C. §1254(1) & (2), ELR STAT. FWPCA §104(1) & (2).

toxicity data, the FDA can then undertake risk assessments, perhaps by class of drug.

Stricter NPDES Permits for POTWs

With regard to PPCPs, as with other pollutants, we need to redouble our efforts toward the CWA's goal of elimination, contained in §101 (a) (6): "It is the national policy that a major research and demonstration effort be made to develop technology necessary to eliminate the discharge of pollutants into the navigable waters, waters of the contiguous zone, and the oceans."[103] NPDES permits and water quality standards offer an opportunity for fine-tuning effluents locally and regionally while problems appropriate to a national solution can be worked out at the agency and legislative levels. There is plenty of room, technologically and legally, for stricter treatment standards at the state POTW permitting level for those states who can brave the political trials and bear the costs of exacting greater treatment. The stricter standards written into a POTW's NPDES permit can be justified by total maximum daily load (TMDL) and water quality provisions. TMDLs can be written for *all pollutant*s. TMDLs and water quality standards are enforceable by states themselves (those with EPA approved permit programs) through the state water quality and TMDL programs. This would seem to give the states most affected by PPCP pollution, which would theoretically include the longest-settled states with the largest population, and those with recycled water programs, as well as states with combined sewers (that would mix farm runoff and household wastewater for example), integrated sewage management and purification systems (that would mix hospital and household wastewater, for example). Moreover, the statutory formula for determining TMDLs includes a component for future growth calculation. This could help address the additional household and industrial pollution, including PPCPs, that new growth brings to a community.

Stricter permits justified by TMDLs and water quality standards are an attractive solution because they are available under current law and can be individually tailored and applied. The permits of POTWs currently discharging PPCP-contaminated effluents could be modified in order to reduce their pharmaceutical emissions, and their discharges could be monitored for a time. Or, in areas where PPCPs are particularly a problem, such is possibly the case in the New Orleans area, a pilot program funded by EPA could pioneer and evaluate the most effective and cheapest technology for PPCP reduction and/or elimination, with tax rebates or other incentives for voluntary participation to achieve an effective upgrade of old domestic delivery systems by municipal water works. When TMDLs are shown to be inadequate, water quality standards[104] are yet another source of protection. Water quality standards are focused primarily on health, and not upon cost of achievement.

Reassessment of POTWs' Secondary Treatment Standards

Preliminary studies of water samples containing PPCPs show that activated charcoal filtration removes up to 90% of the PPCP residues in the subject water samples, at least for most compounds found.[105] This indicates that it may be time for EPA to revisit the requirement, abandoned in 1981, of requiring POTWs to subject wastewater to advanced treatment rather than only secondary treatment. EPA could choose the appropriate technology—activated charcoal filtration, or another technology—that is more effective and more contemporary than sand and other treatments commonly in use. Perhaps EPA might choose to conduct a pilot test program of such technologies in certain states or regions to derive removal efficiency and cost data.

Another solution would be to make POTWs a categorical point source[106] by amending the CWA to give POTWs the status of an industrial category. Whether through reinstating the advanced treatment requirement, or through making POTWs a categorical source, the beneficial end result would be to treat their wastewater to standards that effect greater waste removal, "the greatest degree of effluent reduction which the Administrator determines to be achievable through application of the best available demonstrated control technology, processes, operating methods, or other alternatives, including, where practicable, a standard permitting no discharge of pollutants."[107] An additional benefit of making POTWs a categorical point source would be that (1) new POTWs coming online would be held to stricter standards, and (2) EPA would periodically (every five years) review "as technology and alternatives change" the standards, taking into account the newly available technology, the "cost of achieving such effluent reduction, and any non-water quality environmental impact and energy requirements."[108]

Thus, in evaluating the law and regulations with regard to eliminating PPCPs in surface water through the POTW provisions of the CWA, there is room for improvement, including the presently available possibility of stricter permit standards for individual POTWs, a return to the requirement of advanced treatment of POTW wastes, and/or giving POTWs their own category in the industrial point source scheme.

Solutions Through the SDWA

Since 1944 when the ancestral SDWA was passed, the military/industrial and domestic/material world has changed drastically in the United States. As this Act evolves, and the data regarding toxicity of PPCPs evolve, perhaps MCGLs could be established for the compounds shown to be the most harmful. For example, an initial proposal might be to use the provision regarding estrogenic substances to regulate EDCs in drinking water. Also, highly restrictive (up to zero discharge) MCLGs could be established for substances such as retinoids and antineoplastics/chemotherapy media in amounts that reduce the threat they pose, based upon ex-

103. *Id.* §1251(a)(6), ELR STAT. FWPCA §101(a)(6).

104. *See id.* §1313(d)(1)(A), ELR STAT. FWPCA §303(d)(1)(A). The minimum mandatory water quality standard under the Act is protective of the "fishable/swimmable" use, which takes into account (beyond public water supplies) a standard that protects propagation of fish and wildlife, and recreational uses. *See id.* §1313(c)(2)(A), ELR STAT. FWPCA §303(c)(2)(A).

105. *See* Dunne, *supra* note 8, at 3; Fackelmann, *supra* note 13, at 2.

106. If adopted, POTWs would be the only source not a manufacturer. *See* 33 U.S.C. §1316, ELR STAT. FWPCA §306.

107. *Id.* §1315(a)(1), ELR STAT. FWPCA §305(a)(1).

108. *Id.* §1315(b)(1)(B), ELR STAT. FWPCA §305(b)(1)(B).

isting toxicity data.[109] Until the SDWA and the exposure data regarding PPCPs are further along, the proposals outlined above with regard to the CWA should help reduce the problem of PPCPs in public drinking water.

Proper Drug Disposal

In part, the drugs in sewage were put there deliberately by a misguided effort to throw them away, and thereby prevent their misuse. Although PPCPs are thought to arrive in sewage in far greater quantities through excretion, proper disposal is a means of prevention for PPCP pollution. Proper disposal can be achieved through both a regulatory (in some states)[110] and nonregulatory (educational) means. In states where laws dictate that the toilet is the disposal method of choice, the laws must be changed. The alternatives are most likely throwing them in the trash (landfill) or municipal collection (probably landfill or incineration). Land disposal is not a great choice, but a lesser evil than directing these compounds to the waters of the United States.

Nonregulatory Proposals: Consumer Education and Behavior Modification

Nonregulatory solutions (NRS) include greater public awareness and education, already touched on. The biggest NRS of all is behavioral modification.[111] Both Daughton and Oliver Houck[112] agree that it is a much more effective and efficient use of our time and resources to see that pollutants (such as PPCPs) never enter the water than to spend billions of dollars and years trying to get them out. Regulatory and nonregulatory proposals are not mutually exclusive, but are complementary. Political will can only originate from an informed electorate.

European Proposals

There are further promising suggestions coming from European countries most affected by PPCP pollution and from within the concerned science and environmental communities. Denmark is a relatively small nation geographically (including its water) and in population.[113] Its people consume 34 tons of antibiotics in a year.[114] The detection of PPCPs would be far more threatening in such a context with a more limited drinking water supply. In countries such as Denmark, observers have suggested that the drug approval process automatically include an environmental impact analysis; as in the United States, drugs do not presently include any type of environmental review either before or after their application for manufacture and marketing. Europeans can lead the way in effectively addressing the PPCP problem and spread their influence through global organizations such as the World Health Organization (WHO) and by international agreement.[115]

In Europe, more extensive environmental (including disposal instructions) labeling has also been suggested. The pharmaceutical manufacturer is actually in a highly attractive position to address the problem of PPCP pollution in more innovative ways that interface directly with the consumer, such as environmental informational labeling, or more extensive patient instructions (including how to properly dispose of the medication) either on or inside the packaging or dispensed by the pharmacist when the patient purchases the product. This can be accomplished through voluntary industry measures or through legislation requiring labeling. Either way, it would contribute to good public relations for U.S. drug manufacturers, who are in a highly competitive market that may very well be affected by increasing awareness and purchasing patterns of "green consumerism" worldwide.

The Application of the Precautionary Principle

Inherent in the problem of PPCP contamination is an opportunity to practice a prevention principle as an ethical and guiding priority, following in the footsteps of the original intent of the CWA in its mission to restore and maintain the chemical, physical, and biological integrity of the waters of the United States.

Many authors in the various environmental disciplines have begun to advocate the "precautionary principle." As articulated by EPA's Daughton, this is "the principle of precautionary action that redistributes the burden of proof ('reverse onus') because the science required for truly and fully assessing risks lags far behind the requisite supporting science."[116] The precautionary principle, as an actual pol-

109. *See* Daughton & Ternes, *supra* note 9, at 929. The CWA definition of a "toxic pollutant" is a close fit with EDCs and the worst cases of other pharmaceutical pollution, and may eventually provide a safety net to support a move by EPA to address the filtering out of all pharmaceuticals in wastewater:

> [T]hose pollutants, or combinations of pollutants, . . . which after discharge and upon exposure, ingestion, inhalation or assimilation into any organism, either directly from the environment or indirectly by ingestion through food chains, will, on the basis of information available to the Administrator, cause death, disease, behavioral abnormalities, cancer, genetic mutation, physiological malfunctions (including malfunctions in reproduction) or physical deformations, in such organisms or their offspring.

33 U.S.C. §1362(13), ELR STAT. FWPCA §502(13).

If toxic drug compounds were listed by EPA, this would bring them under 33 U.S.C. §1317(a)(2), ELR STAT. FWPCA §307(a)(2) and its pretreatment standard of best available technology economically achievable.

110. Bouma & Hickerson, *supra* note 6.

111. For an example of recent media attention to the interplay of the environment and human health and how the two are mutually dependent, see Kenny Ausubel, *The Coming Age of Ecological Medicine: Our Health Depends on a Healthy Planet*, UTNE READER, May 8, 2001, *available at* http://www.utne.com/.

112. *See* Oliver A. Houck, *Ending the War: A Strategy to Save America's Coastal Zone*, 47 MD. L. REV. 381-83 (1988).

113. Denmark's area is 42,930 square miles and its population is 5,356,000, according to Lycos Travel, *available at* http://www.lonelyplanet.lycos.com/europe/denmark/destfacts.html.

114. *See* Frank Stuer Lauritsen, *Wanted: Legal Requirements for Environmental Evaluation of Pharmaceuticals*, 11 CHEM. AWARENESS, October 23, 2000.

115. Something like this is in the early stages of achievement. In June 2000, the FDA's branch that deals with veterinary drugs participated in issuing a guidance drafted by the member nations of the International Conference on Harmonization for Veterinary Medicinal Products (VICH) consisting of the European Union, Japan, and the United States, who based the guidance on a collaborative risk assessment regarding veterinary drugs. *See* Velagaleti et al., *supra* note 12. The universe of veterinary drugs is potentially much smaller (in type and quantity) than human PPCPs/EDCs, however.

116. Daughton, Tulane Proceedings, *supra* note 19 at 9-10 (citing also a resource for discussion *at* http://www.biotech-info.net/uncertainty.html).

icy-guiding construct, advocates individual steps throughout decisionmaking, thus acting as a checklist of considerations that ensures that no step is skipped and all decisions are made in a consistent and well thought out manner.

If we do not take the presence of pharmaceuticals in water seriously, and act now to reduce and eliminate their occurrence and reintroduction into the aquatic ecosystem, the results, though highly unpredictable, will certainly be adverse. Such a reduction is achievable through existing or reformed regulatory processes in the FDA and EPA, and by the important reductions achievable through everyday actions of individuals.